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ASSOCIATE VICE PRESIDENT
MANUFACTURING AND QUALITY CONTROL
SCIENTIFIC AND REGULATORY AFFAIRS

PhRMA

July 11, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-0529; Guidance for Industry on Changes to an Approved NDA or ANDA, Notice of Availability; November 23,1999, (64FR65716)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $26 billion in 2000 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

On August 27, 1999 PhRMA submitted extensive comments on the FDA Draft Guidance on this subject in response to the Agency's earlier notice and request for comments of June 28, 1999. Subsequently, the Agency published a final guidance covering the topic in November, 1999. The comments in this letter reflect PhRMA's evaluation of the final guidance that was made available in November, 1999.

The subject guidance is intended by FDA to assist applicants in determining how they should report changes to an approved NDA or ANDA application under the proposed revision to section 314.70 of the drug regulations. The guidance covers recommended reporting categories for post approval changes for drugs, other than specified biotechnology and specified synthetic biological products.

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As sponsors of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), PhRMA members have a long standing interest in and a great deal of experience with the review and approval process for technical manufacturing changes submitted as supplements to approved NDAs and ANDAs.

PhRMA and its members appreciate the generally positive and open scientific dialogue which has developed over the last several years between the industry and the CMC community within FDA. It is our belief that such an open scientific dialogue leads to the most efficient and effective regulatory environment for pharmaceuticals. Following a review of the Final Guidance, PhRMA believes that further discussion is needed regarding the Manufacturing Changes Guidance (Changes to an Approved NDA or ANDA). There are a number of important positive elements in this Guidance relative to regulation and guidance which existed prior to FDAMA. In addition a significant number of improvements were made to the Guidance between June '99 when it issued in draft and the final Guidance of November '99. However, a number of items have been identified which could benefit from continued open scientific dialogue.

Currently, an open discussion of the Guidance has been deemed by the Agency to be excluded by the Good Guidance Practices Guidance. For example, at the FDA Open Hearing on the rule and guidance in August, 1999 the Agency representatives were not allowed to explain their perspectives and interpretations of the Guidance. However, since the rule has recently or will shortly be finalized, the opportunity for dialogue should then be possible and appropriate. PhRMA urges FDA to schedule a meeting at the earliest possible time that would allow a continuation of the dialogue and provide industry with a full understanding of FDA's intent in regard to selected provisions of the Final Guidance..

The small number of items we believe need further discussion are as follows:

1. Synthetic APIs – The Guidance makes no provision for minor process changes prior to the final intermediate which may be annual reportable (e.g., Temp., pH, time). Similarly, no provision is made for anything less than prior approval (PA) for process changes post the final intermediate.

2. Coordination among Guidances - Confusion between example changes provided in the higher level November, 1999 Final Guidance and examples provided in the more detailed and specific SUPAC level guidances is very likely. PhRMA would recommend that as SUPACs are revised and finalized, that the example changes included in the November, 1999 Guidance for the category of changes covered by the new (revised) SUPAC be deleted so that there is not overlapping coverage of the same topic (as was done already for changes to Components and Composition).

3. Extension of Dating – The Guidance's requirement for PA supplements for dating extension with full shelf life data on pilot scale batches is inconsistent with ICH and recent conclusions regarding site specific stability. With the exception of complex dosage forms, dating extensions based on an approved protocol should be annual reportable.

4. Analytical Procedures – The Guidance specifies submission of a supplement (CBE-30) for "Any changes in a regulatory analytical procedure other than editorial or major changes." The high level of detail in typical analytical procedures would mean submission of supplements for many minor changes.

5. Sterile Processing Changes – While sterile products and processes merit a higher level of scrutiny than non-sterile products, the Guidance is unnecessarily broad in listing changes requiring prior approval supplements. For example, re-validations which are repetitions or simple extensions of previously approved validations for these same processes could qualify for reduced reporting. Also, the Guidance as presently written can inhibit manufacturers from making changes which increase sterility assurance since most changes involve the 4 to 6 month implementation delay of a PA supplement.

6. Specifications – The Guidance dramatically increases the scope of the types of specifications that require regulatory reporting via supplements over previous guidances, including microbiological monitoring, packaging components, in-process materials, and all intermediates.

PhRMA would also be pleased to provide a listing of what we determined to be positive improvements in the Guidance and a more detailed discussion of the key issues described above, including recommendations for possible modifications to the Guidance to address those and other issues. That information could be provided as background for a meeting. We look forward to an open scientific dialogue on these topics.

Sincerely,

Thomas X. White

cc: Eric Sheinin, PhD
Helen Winkle
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